The effect of new oral anticoagulants and tranexamic acid on perioperative blood loss and minor bleeding complications following total hip replacement

Summary of Ph.D. thesis

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1. Introduction

Total hip replacement (THR) is one of the most commonly performed orthopaedic procedures, with hundreds of thousands of operations performed each year in the world. It can greatly improve the quality of life for patients with end-stage degenerative disease of the hip. The competing risks of thrombotic events and haemorrhagic complications are amongst the major concerns following hip replacement.

Virchow's triad consists of three factors that may predispose a person to the development of venous thrombosis. All the factors of Virchow's triad might occur in orthopaedic patients during perioperative period: 1) use of tourniquet, immobilization and bed rest cause venous blood stasis; 2) surgical manipulation of the limb cause endothelial vascular injuries; 3) trauma increases the number of thromboplastin agents and use of bone cement increase hypercoagulability. Orthopaedic patients are at the highest risk among all patients for venous thromboembolism (VTE) in terms of perioperative complications. Without any prophylaxis the incidence of deep vein thrombosis (DVT) ranges from 40% to 60% in patients after major orthopaedic surgeries and the incidence of fatal pulmonary embolism (PE) is 2% to 3% after elective THR. Pharmacologic thromboprophylaxis reduces the risk of VTE by more than 60%.

During the last few decades, based on clinical trials, experiences and guidelines, low molecular weight heparins (LMWHs) have become the standard thromboprophylactic drugs in orthopaedics. Enoxaparin, is one of the most favoured subcutaneously administered LMWH in Europe, and was used as the comparator during clinical trials with the new, direct oral anticoagulants (DOACs). Recently the new DOACs for THR have become attractive methods for VTE prevention. In Hungary according to current guidelines and marketing authorizations the available DOACs for VTE prophylaxis in patient undergoing THR are the direct factor Xa inhibitor rivaroxaban and apixaban and the direct thrombin (factor II) inhibitor dabigatran etexilate.

Perioperative anticoagulation, although useful for reducing the significant risk of VTE after orthopaedic surgery, on the other side of the haemostatic equilibrium, all forms of pharmacological prophylaxis increase the risk of perioperative bleeding complications. Allogeneic blood transfusion is a traditional and frequently used method to treat a patient’s low and symptomatic postoperative haemoglobin (Hb) level, however it is well known, that it can potentially extend the rehabilitation time, the length of hospital stay and inhibits the immune system, therefore increases the chance of infection. During the previous decade several studies

have proven the beneficial, blood loss reducing effect of perioperatively administered antifibrinolytic drugs in orthopaedic patients by preventing fibrin degradation and preserving the stable framework of fibrin's structure [8]. Amongst them, the cheap and safe tranexamic acid (TXA) has become a regular part of perioperative protocols in lower limb arthroplasty. Bleeding complications and their consequences should be considered when deciding on the type and time of initiation of the anticoagulation. Personalized risk stratification has become an important part of the new era of VTE prophylaxis to reduce all types of perioperative bleeding risks to the lowest possible level.

Minor bleeding complications related to the surgical wound and to the soft-tissue envelope around the surgical site and their effects on functional outcomes are as significant concerns for orthopaedic surgeons as major bleeding complications are. The wound haematoma following a joint replacement can potentially lead to a periprosthetic joint infection or to joint stiffness and a compromised functional outcome. Examination of these type of complications were neglected previously, however during the last few years they have received increased attention as potentially preventable complications.

2. Aims

The data from development trials suggests that the thromboprophylactic efficacies of the new DOACs are at least equivalent or potentially superior to the clinical trial comparator LMWH, enoxaparin. However, these new agents might be associated with a potentially higher bleeding tendency. Several reviews and trials warned of a potentially higher postoperative bleeding and wound infection rate of DOACs. Our clinical experiences with elevated serous wound discharge enticed us to design a prospective study based on our everyday experience and explore the bleeding profile of DOACs focusing on minor bleeding complications. Clinical trials with dabigatran etexilate for THR focused on major and clinically significant bleeding complications, as safety endpoints, with little attention paid to surgically relevant outcomes, such as wound healing, drainage, and surgical site infection.

1. In Study I our aim was to compare the safety profile of enoxaparin and dabigatran etexilate in the use of primary THR, with particular attention to minor haemorrhagic and soft tissue adverse effects during the early postoperative period.

Most of the studies describing the perioperative major bleeding complication and blood loss reduction effect of TXA, used LMWHs for VTE prophylaxis. Only a very few studies are known to examine TXA's beneficial effect when the new DOACs are used as perioperative anticoagulants in patients undergoing cemented THR. Studies with TXA also neglected to explore its effect on minor bleeding and wound complications.

2. In Study II our aim was to prospectively assess the efficacy of tranexamic acid on postoperative blood loss when rivaroxaban is used as thromboprophylaxis after cemented THR. In addition, we examined the TXA's effect on minor bleeding complication.

3. Materials and methods

Routine preoperative assessment included laboratory tests, such as renal and liver function tests, and coagulation profile. Patients were excluded if they had renal and/or hepatic dysfunction, a history of coagulopathy, previous thromboembolic event, previous cardiovascular implants or bypass surgery, prolonged anticoagulant therapy or extended antiplatelet drug intake (acenocoumarol, warfarin, clopidogrel, acetylsalicylic acid more than 100 milligrams), known epilepsy or allergy to tranexamic acid or to the administered anticoagulant. If patients underwent revision surgery were also excluded from the study. Non-steroidal anti-inflammatory drugs and acetylsalicylic acid ≤100 mg were suspended one week prior to surgery in all patients.

Operations were performed under either general, regional or combined general and regional anaesthesia, depending on the anaesthetic team's decision. All operations were performed by seven consultant orthopaedic surgeons working in a single orthopaedic department, using a direct lateral or Bauer's approach. All operations were performed without utilizing a cell saver or other retransfusion systems. Cefuroxime or clindamycin (in case of confirmed allergy to penicillin) were used as perioperative antibiotic prophylaxis. The intraoperative blood loss was recorded from the contents of the suction canister in the operating theatre. At the beginning of the observational study period (Study I), according to our institutional protocol, two closed suction drains were used for 24hours postoperatively. During the second part of our observational study (Study II) only one intra-articular drain was used for a maximum of 24 hours. To quantify the volume of drainage, it was collected in calibrated and

scaled bottles. The wound and drain sites were covered with the same sized Mepore® bandages after drain removal.

In terms of pain relief, paracetamol, tramadol and metamizole were administered as required. Physiotherapy was started on the first postoperative day with fully weight bearing on the operated lower limb, with restriction of adduction and external rotation.

During the observational study period the effect of the newly introduced medications (anticoagulants and antifibrinolytics) on thrombotic and bleeding complications were examined at our Department. Our main focus was on perioperative blood loss and minor bleeding events, therefore more detailed information were collected in these topics such as bleeding and oozing through the surgical wound, area of skin haematoma and perioperative change in thigh volume. The minor bleeding events and the major and clinically significant bleedings were recorded according to previous publications and guidelines.

3.1. Thrombosis and thromboembolism

In case of a suspected DVT (swelling, excessive oedema, discoloration of the limb or a positive Mayer's or Homans' sign) colour duplex sonography of the affected limb was performed. Clinical suspicion of PE meant an urgent need for computed tomography with pulmonary angiography according to our protocol.

3.2. Major and clinically significant bleeding events

Major bleeding was defined as fatal bleeding; overt bleeding associated with ≥ 20 g/L fall in Hb; overt bleeding leading to transfusion of ≥ 2 units packed cells or whole blood; retroperitoneal, intracranial, intraocular or intraspinal bleeding; bleeding warranting treatment cessation or leading to reoperation. Clinically significant bleeding events were defined as spontaneous skin haematoma ≥ 25 cm^2, wound haematoma ≥ 100 cm^2, spontaneous nose or gingival bleeding > 5 min, spontaneous or intervention associated macroscopic haematuria lasting > 24 h, and any other bleeding event considered clinically significant.

3.3. Minor bleeding events

Minor bleeding was defined as wound bleeding, serous wound discharge and wound haematoma smaller than 100 cm^2.

3.4. Bleeding through the surgical incision and serous wound discharge

Definition of wound bleeding was the bleeding from the surgical wound into the dressing during the first postoperative 24 hours, until drain removal. Its intensity was assessed according to our previously established categories.

Serous wound discharge was defined as the oozing of the surgical wound and drain site after drain removal. The intensity of serous wound discharge was observed. On the 3rd and 7th postoperative days its exact amount was documented according to our previously established categories when wound dressings were checked over the surgical incision and the drain site. The duration of discharge was examined every day, its cessation was precisely documented.

3.5. Skin haematoma

The area of skin haematoma (suffusion) around the surgical wound was measured and patients were categorized according to size.

3.6. Change in thigh volume

Excessive oozing might be associated with increased thigh volume after THR. Jones and Pearson's anthropometric method objectively estimates leg volume by partitioning the leg into six segments which are similar to truncated cones. The upper three truncated cones were used to calculate the thigh volume (mL) by summing up their volumes. Thigh volumes were measured preoperatively and on the 7th postoperative day.

3.7. Calculation of total perioperative blood loss

Study I: The calculated perioperative blood loss (V, mL) was compared between the two groups. For this purpose, the patient's height (H, cm), weight (G, kg) and haematocrit level preoperatively (Hct_0) and on the first postoperative day (Hct_1) were recorded. Patients, who got transfusion in the first 24 h after the operation, were excluded from this calculation. Nadler's formula was used for calculating the perioperative blood loss:

$$\mathbf{V = EBV \times \ln(Hct_0/Hct_1)}$$

Estimated blood volumes (EBV) were calculated with the following formula:

$$\mathbf{EBV = A \times H^{0,725} \times G^{0,425} - B}$$

where A = 0.0236 for men; A = 0.0248 for women; B = 1.229 for men; B = 1.954 for women.

Study II: During Study II, when the blood loss reducing effect of TXA was examined, a different calculation was used, which took into account postoperative haemodilution and transfusion requirement as well. The Hb and Hct levels were measured preoperatively, on the first, second and fifth day after the operation. The blood volume and haemodilution were assumed to normalize on the fifth day. The total perioperative blood loss was monitored as total drop in Hct level on postoperative fifth day compared to the preoperative Hct level. The patient's blood volume (PBV) was calculated using the Nadler's formula as follows:

$$\textbf{PBV (litres)} = (k1 \times \text{height}^3\ (m)) + (k2 \times \text{weight}\ (kg)) + k3,$$

where k1= 0.3669, k2 = 0.03219 and k3 = 0.6041 for men, and k1 = 0.3561, k2 = 0.03308 and k3 = 0.1833 for women.

Multiplying the PBV by the haematocrit (Hct), gives the red blood cell (RBC) volume. Thus a change in the RBC volume can calculated from a change in the Hct level as follows:

$$\textbf{Total RBC volume loss} = \textbf{PBV} \times (\text{Hct}_{\text{pre-op}} - \text{Hct}_{\text{post-op}})$$

The number of units of blood transfused during the hospital stay was recorded. Transfusion (mean volume per unit: 280 mL, mean Hct per unit: 0.55) were taken into account by calculating the total blood loss as follows:

$$\textbf{Total blood loss (litres)} = (\textbf{Total RBC volume loss} + (\textbf{Number of units transfused} \times 0.28 \times 0.55)) / ((\text{Hct}_{\text{pre-op}} + \text{Hct}_{\text{post-op}}) / 2)$$

3.8. Treatment protocols

Study I: We prospectively collected and reviewed all patients undergoing primary cemented THR for osteoarthritis or avascular necrosis of the femoral head from February 2011 until March 2012. These patients were divided into two groups to receive either LMWH enoxaparin (Clexane®, Sanofi-Aventis) or the oral direct thrombin inhibitor dabigatran etexilate (Pradaxa®, Boehringer Ingelheim International). Patients were enrolled in each group according to our weekly altered medication supply: every odd week enoxaparin and every even week dabigatran was administered. Anticoagulants were administered according to the current orthopaedic and manufacturer guidelines. In the enoxaparin group, 40 mg enoxaparin was given

subcutaneously 12 hours before operation and at 8 pm for the next 28-35 days postoperatively. In the dabigatran group, dabigatran etexilate 220 mg was administered for patients below 75 years of age and 150 mg for patients over 75 years of age. Administration was started 4 hours postoperatively with a half-dose (110 mg or 75 mg) and then the full dose was administered once a day at 8 am for 28-35 days after replacement.

Study II: Tranexamic acid was introduced in our Department at the end of 2013, as a perioperative potentially blood-conserving adjunct during primary lower limb arthroplasty. Between January 2014 and November 2014 consecutive patients undergoing primary cemented hip replacement were enrolled in the TXA group. 500 mg TXA was administered intravenously before incision and this dose was repeated 3 hours later, according to current national guideline. These patients were compared with another consecutive patient group from a previous study, who underwent the same procedure prior to the introduction of TXA (control group) from February 2012 until December 2012. All patient data in each observational period was prospectively collected, reviewed and all patients received a primary cemented THR for osteoarthritis or avascular necrosis of the femoral head. In both groups 10 mg rivaroxaban (Xarelto®, Bayer Schering Pharma) was administered as perioperative thromboprophylaxis, started 6 hours postoperatively, then once a day at 8 pm for 28-35 days after joint replacement surgery according to the current orthopaedic and manufacturer guidelines.

3.9. Statistical analysis

In Study I, the statistical analysis was done using t-test, chi-square test and ANOVA with StatSoft® Statistica v.9 statistical software.

In Study II SPSS Statistics 16.0 software was used for statistical analysis. Normal distribution of the data was analysed by the Shapiro-Wilk test. Parametric (Student's T-test) and non-parametric (Mann-Whitney U-test) tests were used for the comparative analyses of data with normal and non-normal distribution, respectively. Categorical variables were analysed by the Chi-square method, with the use of Fischer's exact test, when appropriate.

Results and data are presented in the text as mean (± standard deviation (SD)) or median (interquartile range). The p-values below 0.05 were regarded as statistically significant.

3.10. Ethical approval

Clinical ethics committee approved this study and informed consent was obtained from each participant.

4. Results

Study I: 122 patients were enrolled, 61 into each group. Characteristics of patients in the two group were similar, without no significant differences.

No patients developed clinical features of DVT during the treatment and follow-up period, therefore duplex sonography was not performed. No PE events or deaths occurred during the hospitalization and within 3 months after the operation.

22 patients in the dabigatran group and 21 patients in the enoxaparin group needed transfusion in the postoperative period. No significant differences were found between the two groups in volume of blood loss during surgery: 300 ml (±137.23) in dabigatran group and 314 ml (±197.32) in the enoxaparin group was measured. Volume of the postoperative drainage also did not differ significantly: 470.82 ml (±276.85) in dabigatran group and 471.64 ml (±253.3) in enoxaparin group was found. There were no significant differences in perioperative calculated blood loss, which were 1072.4 ml (±586.6) in the dabigatran group and 1152.3 ml (±486) in the enoxaparin group. No significant differences were found in the total blood loss as calculated by a total drop in preoperative and postoperative first day Hb level: 30.7 g/L (±13.5) using dabigatran and 28.3 g/L (±12.7) using enoxaparin. 8 patients from the enoxaparin group and 3 patients from the dabigatran group received transfusion in the first 24 h after their operations, therefore they were excluded from this calculation and comparison of postoperative Hb drops. Wound bleeding also did not show significant differences between the two groups. There was no statistical significance between groups in the incidence and size of haematoma.

Significant increases of thigh volumes were observed in both groups on the 7^{th} postoperative day compared to preoperative volumes, however, no significant difference was found between the two groups. In contrast to these, the main differences between the two groups were in the duration and intensity of serous wound discharge. Duration of wound discharge was 2.2 (±2.7) days in the dabigatran group and 1.2 (±1.9) days in the enoxaparin group after drain removal ($p<0.05$). Significantly higher intensity of wound draining was found in the dabigatran group ($p<0.05$).

Study II: 81 patients were enrolled in the TXA group, who met our inclusion criteria and got perioperative tranexamic acid. They were compared with 87 patients in the control group. The two groups were statistically identical in terms of patient characteristics.

Three patients in the control group developed clinical features of DVT during their hospital stay, however, colour duplex sonography did not prove our clinical suspicion. No VTE events or deaths were recorded during the study and within the investigated postoperative six week period.

There was no difference in intraoperative blood loss between the two groups: 306.4 mL (±126.6 mL) in the TXA group and 316.7 mL (±170.5 mL) in the control group (p=0.957); however, the postoperative drainage differed significantly: 280 mL (170-350 mL) in the TXA group and 400 mL (300-550 mL) in the control group (p<0.001). The median calculated perioperative blood loss was significantly lower in the TXA group compared to the control group (p<0.001): 1150 mL (780-1496 mL) and 1579 mL (1313-2074 mL), respectively. 12 (15%) patients in the TXA group and 34 (39%) patients in the control group needed transfusion after the operation. The total number of transfused RBC units in the TXA group was 26 versus 82 units in the control group. The mean transfusion rate was significantly lower among the patients where perioperative tranexamic acid was used (0.32 unit (±0.09 unit) versus 0.94 unit (±0.15 unit), p=0.003). The intensity of surgical wound bleeding differed significantly between the two groups during the first postoperative 24 hours: 1.71 (±0.083) in the control group versus 0.35 (±0.086) in the TXA group (p<0.001).

The extent of postoperative thigh swelling showed significant difference on the 7th postoperative day: 270.3 mL (129-449 mL) in the TXA group and 539.8 mL (350.0-864.8 mL) in the control group (p<0.001). The size of haematoma was significantly smaller in the TXA group (0.64 (±0.21) vs. 2.46 (±2.13), p<0.001). The duration of serous wound discharge after drain removal had a tendency to be shorter in the TXA group (0.56 day (±0.97 day)) compared to the control group (1.15 day (±1.86 day), which did not reach the statistical significance (p=0.064). Significant thigh volume increase was found in the control group on the 7th postoperative day (p<0.001).

5. Discussion

Study I: Our clinical experiences with elevated serous wound discharge enticed us to examine the bleeding profile of dabigatran focusing on minor bleeding events and design a prospective study. No previous similar detailed reports are available with dabigatran on the minor, but clinically important, potentially detrimental side effects. A previous study in the United Kingdom found a significant, delayed wound discharges after taking dabigatran

postoperatively. Based on their study they no longer administer dabigatran from the day of surgery but prefer to start the VTE prophylaxis with dalteparin (LMWH) until the wound is dry postoperatively and then discharge the patient home on oral dabigatran.

In our study the incidence of major and clinically significant bleeding events were higher in both groups compare to the dabigatran development trials, although the same previous guidelines were applied. Although our study involved a relatively small number of patients, we have managed to find significant differences in serous wound discharge. No such differences were found in terms of skin haematoma formation. Only a few studies examined the wound complication rate using dabigatran, our study was among the first ones. Our aim was not to establish the pharmacological explanation for minor bleeding complications. We can only hypothesise that the relatively early postoperative administration of dabigatran (starting with a half dose 1-4 hours after surgery), might be responsible for the increased incidence of postoperative wound ooze. The current American College of Chest Physicians guidelines recommend to start LMWH as thromboprophylaxis either 12 hrs or more preoperatively or 12 hrs or even later postoperatively rather than within 4 hrs or less preoperatively or 4 hrs or less postoperatively. Also there are publications supporting this theory about an elevated incidence of bleeding complications and wound infection using rivaroxaban (started 6-10 hours after surgery).

We found the same, statistically significant increase in thigh volume in both our groups between the initial and 7th postoperative day data, without any difference in thigh volumes with the two different anticoagulants. These increased thigh volumes might be caused by the normal wound healing processes which are regulated by local proinflammatory cytokines, growth factors, tissue response processes and are also related to the hidden blood loss that might be present during major orthopaedic interventions. A recent study examined histologically the effect of enoxaparin, rivaroxaban and dabigatran on wound healing process using a rat model, and found neither beneficial nor harmful effect of them on wound healing. An early study in 1981 mentioned anticoagulant therapy causing wound haematoma and wound draining as risk factor of deep infection after THR. It is still controversial whether a wound leakage can be an important source of late periprosthetic infection, however some authors observed positive correlation between discharge from the wound and late deep infection. The first report on minor, but clinically important side-effects found an increased incidence of bruising and prolonged discharge from the drain site after enoxaparin compared to control group without thromboprophylaxis. Over the last two decades we have come to accept the minor side-effects

of enoxaparin. The new dabigatran etexilate can potentially cause more prolonged oozing from the drain site and an increased incidence of serous wound discharge, which might prevent this agent from being widely used in orthopaedic surgery. Additional to this, it is unsafe to discharge a patient with an oozing wound or drain site, even when his/her postoperative state would otherwise allow this, which might lead to longer hospitalisation and prolonged use of antibiotics to prevent secondary contamination of the surgical site.

Study II: A handful of studies have examined peri- and postoperative bleeding after THR with the use of tranexamic acid. Regarding cemented THR, the femoral canal and the acetabular bony beds are closed off by bone cement, and its pressurization has a ceasing effect on blood loss from the intramedullary circulation. Therefore, postoperative bleeding tends to be lower in cemented THR compared to cementless THR, which means that it is essential to examine the two types of prosthesis separately. Our study was amongst the first few orthopaedic studies publishing results on the effect of TXA following THR when the new oral anticoagulant rivaroxaban was used for thromboprophylaxis. According to our knowledge, this study was the first prospective study examining the effect of TXA in primary cemented THR using rivaroxaban as thromboprohylaxis and focusing on minor bleeding and wound leakage complications.

Regarding cemented THR, the timing and dosage of TXA are still subject to an intense debate. In Hungary, the use of a daily dose of 500-1000 mg intravenous TXA is approved for prophylaxis to prevent local fibrinolysis.

According to a recently published meta-analysis, involving 1608 patients undergoing THR from 25 randomized controlled trials and reported on wound complications, the use of TXA leads to a slight reduction in the risk of developing wound complications compared to the control group [54]. We found the same, in our patients who received TXA, there was significantly reduced wound bleeding, a smaller frequency of wound dressing changes, and had a tendency to achieve a dry surgical wound earlier as compared with the control group. In the TXA-group, the extent of thigh swelling was 50% less on the 7^{th} postoperative day, which can be attributed to the reduced formation of a deep haematoma. Our study examined the superficial haematoma on the skin surface as well, which was significantly smaller in size when compared with the control group. In a previous double-blinded, randomized study, deep haematoma volumes were measured with ultrasonography on the 7^{th} postoperative day in a group of patients receiving TXA and a control group not receiving TXA following THR. The authors did not find a significant difference; however, the mean volume of haematoma was 28% smaller in their

TXA group (270 mL (CI 209-331 mL) vs. 376 mL (CI 257-494 mL)). These findings can be explained by the pharmacological effect of TXA, as revealed in an early in vitro study, where the authors found that tranexamic acid inhibited clot lysis more efficiently when it was added before clot formation.

Previous studies have examined the factors which can cause prolonged wound healing and late periprosthetic infection. The postoperative haematoma formation and thigh swelling were found among the potential sources of infectious complications. A limitation of our study was a relatively small sample size, and therefore it was not powered to examine relatively rare complications such as periprosthetic joint infection. However, it provided evidence of a reduced presence of potential predisposing factors of infectious complications in patients receiving TXA.

One of the limitations was the perioperative administration of a total of 1000 mg TXA, which is lower dose than what used in some of the prior studies. Despite this arguably low dose, we found a significantly reduced postoperative blood loss, transfusion rate and decreased wound bleeding in the TXA treatment group, suggesting sufficient serum levels. Our study did not use randomisation; however, the two groups were clearly separated in time, and the only variable distinguishing the two groups was the use of TXA. In addition to the demonstrated decrease in the need of transfusions, the decreased incidence of minor bleeding complications may have the potential to provide an additional benefit in reducing the frequency of delayed infectious complications.

6. Conclusions

The new findings of the above presented works can be summarized as the following:

1. Increased incidence of prolonged discharge from the drain site and elevated serous wound discharge were found using dabigatran if compared with enoxaparine.

2. The same amount of thigh volume increase was observed on the 7th postoperative day after THR with either enoxaparine, dabigatran or rivaroxaban.

3. According to our knowledge, we reported the first clinical study examining the effect of perioperatively administered TXA in a well-defined subgroup of patients undergoing clearly cemented THR and anticoagulated postoperatively with rivaroxaban.

4. The extent of thigh swelling was about 50% less on the 7th postoperative day, when TXA was used perioperatively during THR.

5. In addition to the well-known perioperative blood loss and transfusion rate reducing effect of TXA, our results demonstrate a significant reduction of postoperative minor bleeding complications using multiple end-points. Using TXA we can reduce the blood loss through drainsite, the surgical wound bleeding, the size of superficial haematoma and we can achieve a dry surgical wound earlier.

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I dedicate this work to the memory of the late Professor Kálmán Tóth.

List of peer-reviewed scientific publications related to the thesis

I. **Gombár C.,** Horvath G., Gálity H., Sisák K., Tóth K. Comparison of minor bleeding complications using dabigatran or enoxaparin after cemented total hip arthroplasty. **Archives of Orthopaedic and Trauma Surgery, 2014;134(4): 449-457.**

IF: 1.597 Q1

II. **Gombár C.,** Gálity H., Győrfi G., Sohár G., Sisák K., Tóth K. Dabigatran és enoxaparin használata során nyert tapasztalataink csípőprotézis beültetést követően [Our experiences with the use of dabigatran and enoxaparine as thromboprophylactic agents following primary total hip replacement] **Magyar Traumatológia, Ortopédia, Kézsebészet, Plasztikai Sebészet 2015;58(1):51-62.**

III. **Gombár C.,** Gálity H., Bácsi M., Sisák K. A tranexámsav vérvesztést és kis vérzéses szövődményeket befolyásoló hatása cementes csípő protézis beültetés után [Effect of tranexamic acid on blood loss and soft-tissue swelling following cemented total hip replacement] **Orvosi Hetilap 2019;160(12): 456–463.**

IF: 0.497 Q3

Total impact factor of original papers related to the thesis: 2.094

List of scientific publications not related to the subject of the thesis

I. **Gombár C**, Tóth K, Kellermann P. Effect of calcaneal-stop procedure on load conditions of pediatric flexible flatfoot **Fiziologia-Physiology, Official Journal of the Romanian Society of Physiological Sciences**, 2011. supplement, Abstract volume ISSN 1223-2076

II. Sohár G, **Gombár C**, Gálity H, Tóth K. Veleszületett dongaláb Ponseti szerinti kezelésével elért kezdeti eredményeink [Early results of the Ponseti method for the treatment of congenital clubfoot disease] **Magyar Traumatológia, Ortopédia, Kézsebészet, Plasztikai Sebészet** 2012;55:(1-2) pp. 67-72.

III. **Gombár C**, Janositz G, Friebert G, Sisák K. The DePuy Proxima™ short stem for total hip arthroplasty – Excellent outcome at a minimum of 7 years **Journal of Orthopaedic Surgery** 2019;27(2):1–6. *DOI: 10.1177/2309499019838668*

IF: 1.095 Q2

IV. Friebert G, **Gombár C**, Sisák K. Kiterjedt acetabularis csontdefektusok (Paprosky 3B medence diszkontinuitással) kezelése impaktált csont allograft és ilioischialis cage használatával [Treatment of extensive acetabular bone defects (Paprosky 3B with pelvic discontinuity) with the use of impaction bone grafting and ilioischial cage] **Magyar Traumatológia Ortopédia Kézsebészet Plasztikai Sebészet**, 2020. 63. évf. 1–2. (accepted, in press)

V. Sisák K, **Gombár C**, Friebert G, Koós Z. Modern treatment of recurrent patellofemoral instability - combined medial patellofemoral ligament reconstruction and tibial tubercle transfer **Acta Chirurgiae Orthopaedicae et Traumatologiae čechoslovaca** 2020; 87(6) p. 396 – 403 PMID: 33408004.

IF(2019): 0.198 Q4

VI. Friebert G, **Gombár C**, Bozó A, Polyák I, Brzózka Á, Sisák K. Differences between proximal bone remodeling in femoral revisions for aseptic loosening and periprosthetic fractures using the Wagner SL stem **BMC Musculoskeletal Disorders** 2021 Feb 17;22(1):201. doi: 10.1186/s12891-021-04062-6.

IF(2019): 1.879 Q2

Cumulative impact factor: 5.266